REMARKS

In general, Applicant's invention features a method for C-terminal protein tagging. The method begins with a nucleic acid sequence that encodes the protein to be tagged. The nucleic acid is translated under conditions that result in stalling of translation at the 3' end of the protein coding sequence, thereby forming a stalled translation complex. To generate the tagged protein, this complex is then contacted with a puromycin-tag under conditions that allow the puromycin-tag to be covalently bonded to the protein's C-terminus. Stalling translation at the 3' end of the nucleic acid sequence prior to contact with the puromycin-tag is an important aspect of Applicant's method. As noted in the present specification, for example, at page 12, line 14 - page 13, line 17, bonding of the puromycin-tag to the protein following translation stalling maximizes the yield of C-terminally tagged protein product.

Summary of the Office Action

Claims 14-31 are pending (claims 1-13 having been canceled by the present amendment). Claims 14-16, 19-26, and 28-31 stand rejected, under 35 U.S.C. § 102(e), as being anticipated by Yanagawa (U.S. Patent No. 6,228,994), and claim 27 stands rejected, under 35 U.S.C. § 103, as being anticipated by Yanagawa in view of Schatz et al. (U.S. Patent No. 5,723,584). Objections have also been raised to the drawings. Each of these issues is addressed below.

Support for the Amendment

Claim 29 has been amended to clarify claim language. Support for this amendment is found in the specification, for example, at page 9, lines 15-23. No new matter has been added by this amendment.

Objection to the Drawings

In response to the objection to the drawings, Applicant submits herewith a set of formal figures in which all defects have been corrected. These figures satisfy 37 C.F.R §§ 1.84 and 1.152, and this objection may be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 14-16, 19-26, and 28-31 stand rejected, under 35 U.S.C. § 102(e), as being anticipated by Yanagawa (U.S. Patent No. 6,228,994). This rejection is respectfully traversed.

To support a *prima facie* case of unpatentability under § 102, a single prior art reference must describe all of the elements and limitations of the rejected claim. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdtn. v. Genentech, Inc.* 927 F.2d 1565, 1576 (Fed. Cir. 1991). The Office has not met this burden of proof because the method taught in the '994 patent differs in a

fundamental respect from the method of claim 14. Claim 14 requires that *translation stalls at the 3' end of the nucleic acid sequence, forming a stalled translation complex comprising the protein* and that *the stalled translation complex is contacted with the puromycin-tag*. The method taught in the '994 patent never teaches a method with these two steps.

The Examiner acknowledges that "Yanagawa *et al.*, did not directly show to form a stalled translation complex, recited in step (b) of the claim" (Office Action, page 3) and also that "normally there is no translation complex after translation terminates" (Office Action, page 6).

This rejection therefore rests wholly on the assertion that "in the absence of convincing evidence to the contrary, a translation complex *before addition of a puromycin* (before peptide was released) *are considered as a stalled translation complex* since there was a time period that a synthesized protein waited for the puromycin to be added even through [sic] this complex only existed in [sic] very short time. The peptide was released based on addition of the puromycin (see the attachment)." This assertion is incorrect.

First, Applicant points out that it is only in the *present application* that translation is allowed to occur without any puromycin in the translation reaction, as described by the Examiner. The present application discloses that the mRNA used for translation is modified at the end of the protein coding region to cause translation to stall, and that, after this occurs, puromycin is then added to the translation reaction to tag (label) the

proteins.

In contrast, the Yanagawa '994 patent discloses a method of translation in which puromycin is added at the *start of translation* (Yanagawa, Col. 5, lines 24-35; Col. 5, line 65 to Col. 6, line 10; and in the examples at Col. 10, lines 1-8). Thus, the '994 patent does not teach nor can it be shown to be inherent in the '994 method that (as quoted above) "a translation complex *before addition of a puromycin* (before peptide was released) are considered as a stalled translation complex since there was a time period that a synthesized protein *waited for the puromycin to be added* even through [sic] this complex only existed in [sic] very short time." In Yanagawa, puromycin was present during the entire reaction. Thus, not only doesn't Yanagawa teach a stalled translation complex, it is impossible for such a complex to have simply "occurred" because puromycin was withheld from the *in vitro* translation reaction mixture -- the puromycin was present the entire time.[1] The Office's rationale is therefore neither disclosed nor supported by the Yanagawa '994 patent, and the rejection of claims 14-16, 19-26, and 28-31 under 35 U.S.C. § 102 rejection should be withdrawn.

Further, with respect to claim 29, the Office states that this claim is also anticipated by Yanagawa because "fluorpur or fluorthiopur tag (see Figure 2) was be considered as a phenyl diboronic derivative" (Office Action, page 7). This rejection should also be withdrawn. As previously pointed out by Applicant, these Yanagawa

1 Applicant further states, for the record, that no support has been provided by the Office for the contention that a stalled translation complex *would* be formed simply by carrying out the translation reaction in the absence of puromycin.

compounds cannot anticipate claim 29, because neither includes a boron. To clarify this requirement in claim 29, the claim has been reworded to specify that the specific binding pair member recited in the claim "comprises a phenyl diboronic acid moiety." Because neither fluorpur nor the fluorthiopur tag includes a phenyl diboronic acid moiety, the rejection of claim 29 should be withdrawn.

Rejection under 35 U.S.C. § 103

Claim 27 stands rejected, under 35 U.S.C. § 103, as being unpatentable over a combination of Yanagawa (U.S. Patent No 6,228,994 B1) and Schatz et al. (U.S. Patent No. 5,723,584). This rejection is also respectfully traversed.

With respect to the primary reference Yanagawa, the Office is directed to Applicant's discussion presented above. As indicated, Yanagawa does not disclose or suggest a method of C-terminal protein tagging that makes use of a stalled translation complex. In fact, the '994 patent teaches away from this step, teaching that the tag is introduced *at the beginning of the reaction* and attached during active protein synthesis. Moreover, Yanagawa's methods are limited to standard transcription/translation reactions using standard nucleic acid templates. Yanagawa does not suggest that the disclosed approaches for protein labeling might be improved, and certainly does not lead one skilled in the art to use a stalled translation complex in the protein labeling reaction.

The other cited reference, Schatz et al., as acknowledged by the Examiner, also

does not provide this teaching. The Office agrees that "Schatz does not discuss any method remotely related to Applicant's claimed method for C-terminal protein tagging, nor does it discuss the use of stalled translation complexes in any context." Schatz therefore cannot provide what Yanagawa lacks -- a method for C-terminal tagging that makes use of a stalled translation complex. The § 103 rejection of claim 27 should be withdrawn.

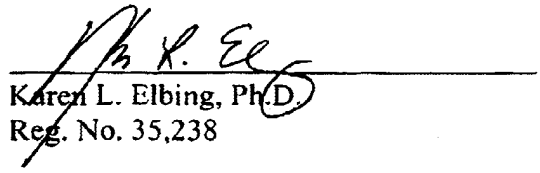
Conclusion

Applicant submits that this case is in condition for allowance, and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 29 April 2003



Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045